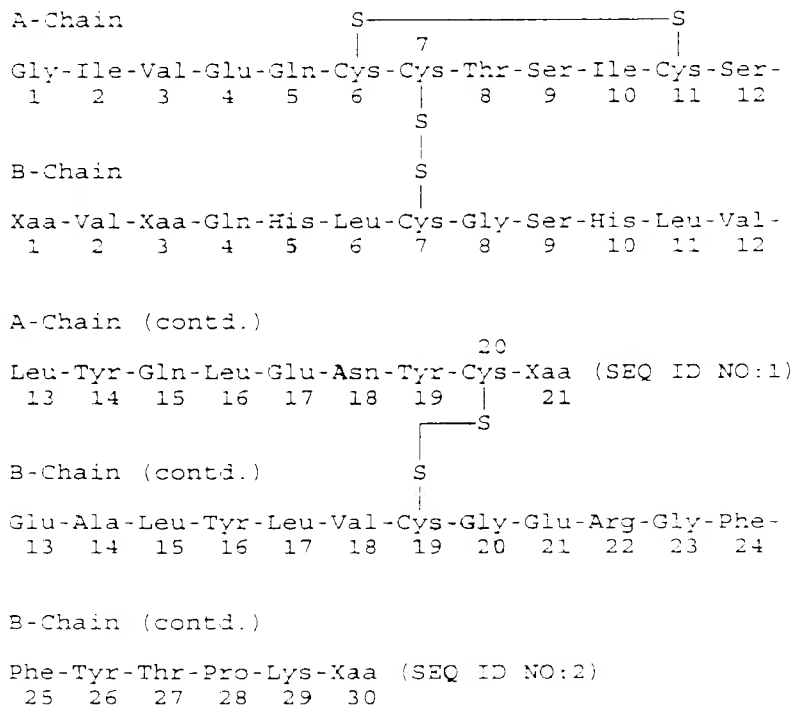
CLAIMS

1. An insulin derivative having the following sequence:



wherein

(a) Xaa at positions A21 and B3 are, independently, any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys;

(b) Xaa at position B1 is Phe or is deleted;

(c) Xaa at position B30 is any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys; and

(d) the ε-amino group of Lys^{B29} is substituted with a lipophilic substituent having at least 10 carbon atoms;

wherein the insulin derivative is a Zn^{2+} complex and the Zn^{2+} complex of the insulin derivative is more water soluble than the insulin derivative without Zn^{2+}.

3. The insulin derivative [illegible]

4. The insulin derivative according to claim 1, wherein Xaa at position A21 is Ala, Asn, Gln, Gly or Ser.

5. The insulin derivative according to claim 4, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

6. The insulin derivative according to claim 1, wherein Xaa at position B1 is deleted.

7. The insulin derivative according to claim 6, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

8. The insulin derivative according to claim 1, wherein Xaa at position B1 is Phe.

9. The insulin derivative according to claim 8, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

10. The insulin derivative according to claim 1, wherein Xaa at position B3 is Asn, Asp, Gln or Thr.

11. The insulin derivative according to claim 10, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

12. The insulin derivative according to claim 1, wherein Xaa at position B30 is Ala or Thr.

13. The insulin derivative according to claim 12, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

14. The insulin [illegible]

16. The insulin derivative according to claim 1, wherein Xaa at position A21 is Asn, Xaa at position B3 is Asn, Xaa at position B1 is Phe and Xaa at position B30 is Thr.

17. The insulin derivative according to claim 16, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

18. The insulin derivative according to claim 1, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

19. The insulin derivative according to claim 1 which is in the form of a hexamer.

20. The insulin derivative according to claim 19, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

21. The insulin derivative according to claim 19, wherein Xaa at position A21 is Asn, Xaa at position B1 is Phe, Xaa at position B3 is Asn, and Xaa at position B30 is Thr.

22. The insulin derivative according to claim 19, wherein two zinc ions bind to the hexamer.

23. The insulin derivative according to claim 22, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

24. The insulin derivative according to claim 19, wherein three zinc ions bind to the hexamer.

25. The insulin derivative according to claim 24, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

28. A pharmaceutical composition which is an aqueous solution, comprising (a) an insulin derivative according to claim 1, (b) an isotonic agent, (c) a preservative and (d) a buffer.

29. The pharmaceutical composition according to claim 28, wherein the pH of the aqueous solution is in the range of 6.5-8.5.

30. The pharmaceutical composition according to claim 28, wherein the solubility of the insulin derivative exceeds 600 nmol/ml of the aqueous solution.

31. The pharmaceutical composition according to claim 28, further comprising an insulin or an insulin analogue which has a rapid onset of action.

32. The pharmaceutical composition according to claim 28, wherein Xaa at position A21 is Asn, Xaa at position B3 is Asn, Xaa at position B1 is Phe and Xaa at position B30 is Thr.

33. The pharmaceutical composition according to claim 28, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

34. The pharmaceutical composition according to claim 28, wherein the insulin derivative is in the form of a hexamer.

35. A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of a pharmaceutical composition according to claim 28.

36. An insulin derivative having the following sequence:

A-Chain S———————S

Gly-Ile-Val-[illegible]

A-Chain (contd.)

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                                    20
Leu-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys-Xaa (SEQ ID NO:1)
 13  14  15  16  17  18  19   |   21
                              S
                              |
B-Chain (contd.)              S
                              |
Glu-Ala-Leu-Tyr-Leu-Val-Cys-Gly-Glu-Arg-Gly-Phe-
 13  14  15  16  17  18  19  20  21  22  23  24
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B-Chain (contd.)

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Phe-Tyr-Thr-Pro-Lys-Xaa (SEQ ID NO:2)
 25  26  27  28  29  30
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wherein

(a) Xaa at positions A21 and B3 are, independently, any amino acid residue which can be coded for by the genetic code except Lys, Arg and Cys;

(b) Xaa at position B1 is Phe or is deleted;

(c) Xaa at position B30 is deleted; and

(d) the ϵ-amino group of Lys^{B29} is substituted with a lipophilic substituent having at least 10 carbon atoms;

wherein the insulin derivative is a Zn^{2+} complex and the Zn^{2+} complex of the insulin derivative is more water soluble than the insulin derivative without Zn^{2+}.

37. The insulin derivative according to claim 36, wherein Xaa at position A21 is Ala, Asn, Gln, Gly or Ser.

38. The insulin derivative according to claim 37, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

39. The insulin derivative according to claim 36, wherein Xaa at position B1 is deleted.

40. The insulin derivative according to claim 39, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

43. The insulin derivative according to claim 36, wherein Xaa at position B3 is Asn, Asp, Gln or Thr.

44. The insulin derivative according to claim 43, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

45. The insulin derivative according to claim 36 wherein Xaa at position A21 is Ala, Asn, Gln, Gly or Ser, and Xaa at position B3 is Asn, Asp, Gln or Thr.

46. The insulin derivative according to claim 45, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

47. The insulin derivative according to claim 36, wherein Xaa at position A21 is Asn, Xaa at position B1 is Phe, and Xaa at position B3 is Asn.

48. The insulin derivative according to claim 47, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

49. The insulin derivative according to claim 36, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

50. The insulin derivative according to claim 36 which is in the form of a hexamer.

51. The insulin derivative according to claim 50, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

52. The insulin derivative according to claim 50, wherein Xaa at position A21 is Asn, Xaa at position B3 is Asn, and Xaa at position B1 is Phe.

55. The insulin derivative according to claim 50, wherein three zinc ions bind to the hexamer.

56. The insulin derivative according to claim 55, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

57. The insulin derivative according to claim 50, wherein four zinc ions bind to the hexamer.

58. The insulin derivative according to claim 57, wherein the lipophilic substituent has from 12 to 24 carbon atoms.

59. A pharmaceutical composition which is an aqueous solution, comprising (a) an insulin derivative according to claim 36, (b) an isotonic agent, (c) a preservative and (d) a buffer.

60. The pharmaceutical composition according to claim 59, wherein the pH of the aqueous solution is in the range of 6.5-8.5.

61. The pharmaceutical composition according to claim 59, wherein the solubility of the insulin derivative exceeds 600 nmol/ml of the aqueous solution.

62. The pharmaceutical composition according to claim 59, further comprising an insulin or an insulin analogue which has a rapid onset of action.

63. The pharmaceutical composition according to claim 59, wherein the insulin derivative is a Zn^{2+} complex.

64 The pharmaceutical composition according to claim 59, wherein Xaa at position A21

which has from 12 to 24 carbon atoms

66. The pharmaceutical composition according to claim 59, wherein the insulin derivative is in the form of a hexamer.

67. A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of a pharmaceutical composition according to claim 59.